



Particularities of Chronic Urticaria in Latin American Countries: Epidemiology, Pathogenesis and Treatment

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Accepted: 29 October 2024
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Abstract

Purpose of Review Chronic Urticaria is a multifactorial disease. Despite international guideline recommendations each region has particular characteristics with unique needs. The aim of this review is to present the particularities of urticaria in Latin America (LATAM) and evaluate the clinical and investigation costs of CSU in LATAM and other regions.

Recent Findings In the last 10 years there has been a significant increase in research on CSU in LATAM. At the molecular level, the presence of specific IgE against environmental allergens and eosinophils seems to be more frequent among CSU in LATAM than in other regions, suggesting a greater presence of type 2 inflammation, perhaps secondary to the characteristics of the environment in some areas of LATAM. At a clinical level, there are common points and differences with respect to what has been published in other regions, especially in terms of management secondary to economic access barriers.

Summary It is important to understand the causes of these particularities to modify those that result in a high cost for the patient and society.

Keywords Angioedema · Antihistamines · Pathogenesis · Cost · Omalizumab · Urticaria

Introduction

Chronic Spontaneous Urticaria (CSU) has a high cost for the patient and the society. By June 2024, when entering the words “Chronic Urticaria” in PubMed in the last 10 years, a total of 3,515 original articles appeared. The increasing number of CSU articles in the last ten years reflects the broad interest that the disease has in the medical and scientific community. Latin America (LATAM) represents 6% of the world's population but only 3% of published articles are conducted with population from the region, which highlights

an important gap in knowledge of the disease in this part of the world. Despite this gap in knowledge, some studies published in the last 10 years provide epidemiological and mechanistic information that allow us to understand the impact of international recommendations on medical management in CSU patients from LATAM.

In this article, we present a detailed review of the CSU in LATAM, we also present the identified knowledge gaps and potential solutions. The different topics covered are developed from some questions regarding different areas of knowledge of the CSU.

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CSU publications from Latam

What information is there about CSU in LATAM? To answer the following question, we conducted a search of original articles published about chronic urticaria (CSU or Chronic inducible urticaria: CIndU) from LATAM population in the last 14 years (Fig. 1). We included articles from PubMed, Google Scholar, and LILACs database (Latin American Caribbean Literature in Health Sciences). The period included for the search was January 1, 2010, to June 20, 2024. The keywords used were: Urticaria, Hives, Angioedema,



Fig. 1 CSU publications in LATAM 2010 to June 2024. **A)** total number of original CSU articles published in PubMed and LILACs database from January 2010 to June 2024. **B)** Number of original

published investigations reviewed. **C)** LATAM distributions by countries of published articles in LATAM during January 2010 to June 2024 according to the selection criteria

Anaphylaxis, antihistamines, Omalizumab, Clinical trials, peroxidase, hypothyroidism, Comorbidities. Latin America, and the name of each LATAM country.

Additionally, we conducted surveys with several Allergists and Dermatologists in the region to identify possible barriers to access to treatment and gaps in knowledge. The barriers and gaps were synthesized and stratified according to their impact on the entire region or in each particular country.

With this search system we found 948 articles but only 361 were original articles, which is lower than the number of articles published during the same period in Europe ($n = > 1000$) or North America ($n = > 1000$), but similar to what was published in China ($n = 377$) or Japan ($n = 286$). Thirty-three countries make up LATAM (Fig. 1): fourteen LATAM countries have published information about CSU in the last 14 years; only 7 countries have more than 10 publications about CSU (Argentina, Brazil, Colombia, Ecuador, Mexico, Peru and Venezuela).

Knowledge gap Most of the studies published in LATAM are descriptive and few are multicentric, which would allow direct comparisons to be made between the various populations in the region.

Recommendation Collaborative work between the 19 LATAM centers of excellence in urticaria (UCARE network <https://ga2len-ucare.com/centers/>) can improve the quality of research in the region and the performance of multicentric studies.

Epidemiology

What is the prevalence of CSU in LATAM? Currently only Brazil has population studies evaluating the prevalence of urticaria; Balp et al. found a prevalence of 0.41% among those over 18 years of age [1]. Among urticaria specialists (allergists and dermatologists) 3% to 17% of clinical appointments are due to chronic urticaria [2–5]. There is not enough information in LATAM about the prevalence in childhood, but one study in an allergy center reported that 4/10 patients who consulted for urticaria symptoms were children [4] which suggests that the prevalence could be higher than that reported in other regions [6].

What are the characteristics of the CSU patients from LATAM? Similar to what has been reported in other regions, in LATAM there is a clear predominance of the disease in the female gender with a ratio of 2:1 to 4:1 [4, 7–11]. The predominant age of onset is in the third to fifth decade of life [4, 7–11]. However, almost all studies included only patients over 18 years of age, therefore information about the prevalence and characteristics in children is unknown. Similar to other regions, hypothyroidism is more frequent in CSU patients than in the general population with a prevalence associated with patient age [12–14]. CIndU occurs concomitantly in 30% to 60% of the CSU patients; the frequency depends on the diagnostic criteria [10, 15]. A study conducted in Colombia evaluated the frequency of CIndU among patients with CSU using challenge tests and observed a self-report of 70% versus only 33% confirmed by challenge tests [10].

What is the evolution of the disease? Two studies explored the clinical evolution of CSU in LATAM. A study carried out in Colombia reported, after follow-up for 5 years, a clinical remission rate without the need for pharmacological treatment of 59% and a relapse rate of 17% in the same period. Likewise, in this study it was reported that up to 11% of CSU patients could progress to pruritus without hives or angioedema. These diverse forms of evolution suggest that the initial causes of CSU could define the course of CSU to persistence or to CSU remission over time [14, 16, 17]. Another study observed that among patients who had CSU and also NSAID-hypersensitivity, in those who achieved clinical CSU remission without treatment, more than 60% also achieved tolerance to the consumption of NSAIDs, which has great importance for the management approach and removal of unnecessary restrictions [18].

Are there clinical differences between LATAM populations? There are few studies that included patients from different LATAM populations. The AWARE study included information from several countries and made a comparison with information obtained from European countries [3]; The sociodemographic and clinical characteristics between Latin American and European countries were similar, with a small but significant difference in the frequency of CIndU (73% European countries versus 65% LATAM) and UCT (7.8 points versus 7.2 points). Unfortunately, the study did not make a comparison between Latin American countries. A study in two cities in Colombia (Medellín and Bogotá) compared the frequency of CIndU, observing that despite sharing genetic ancestry, these two populations presented statistically significant differences in the prevalence of dermatographic CIndU and cold CIndU. In the more temperate city there was a lower frequency of cold CIndU while in the warmer city the dermographism CIndU was lower. These differences indicate that the environment could influence CSU phenotypes, which should be explored in future research [3, 10].

Knowledge gap Studies are needed comparing different LATAM populations to evaluate whether behavior is homogeneous or presents changes according to the particular conditions of each Latin American country.

Recommendation Conducting sociodemographic studies in LATAM would allow us to compare the different populations in the region and identify factors associated with the disease and different clinical outcomes of interest.

Pathogenesis of CSU in LATAM

Are there genetic patterns in CSU patients from LATAM? Calamita et al. evaluated the involvement of the major histocompatibility complex classes I and II (loci A, B and DR) in Brazilian CSU patients but there was no specific association between the HLA alleles studied and chronic urticaria [19]. Silveiras et al., observed association between thyrotropin receptor gene expression, CSU urticaria, and Hashimoto's thyroiditis [20]. More gene pattern studies are needed in the Latin American population to identify genes associated with the disease or with clinical outcomes of interest.

Are there molecular patterns in CSU patients from LATAM? Some studies in LATAM demonstrated that type 1 and type 2b autoimmunity are present but in different proportion than other regions [21]. Sánchez J et al., observed that autoantibodies directed against thyroperoxidase (TPO) were present in 36% of CSU patients: This group also detected IgE antibodies against eosinophilic proteins type ECP (26%) and EPX (28%) (ECP: Eosinophil Cationic Protein and EPX: Eosinophil peroxidase) [13, 14, 17]. Between 30 to 48% of CSU patients have eosinophilic infiltration in hives [22, 23]. European studies suggest that low levels of total IgE (< 75 IU/ml) as well as low levels of anti-TPO IgG could be associated with type 2b autoimmunity, while elevated total IgE could be associated with type 1 autoimmunity [24]. There are studies that suggest that low levels of Eosinophils in the blood (< 50 cells/ml) are associated with a particular inflammatory profile in CSU [25, 26]. In the general population of several LATAM countries, the levels of total IgE and eosinophils are usually much higher than those reported in European countries and some regions of China [15, 27–29]. Population from some cities in Mexico and Colombia, the average serum total IgE levels sometimes exceeds 200 IU/ml even in the general population and median eosinophil count is over 150 cells/ml in 15% to 30% of the population [29–31]. These particularities of some countries in the region indicate that the application of potential biomarkers detected in other populations must undergo diagnostic performance tests before their general use or that perhaps the cut-off points must be recalculated. The high levels of total IgE and blood eosinophils in LATAM populations may be due to the persistence of some endemic parasitic infections in the region that pressure a type 2 inflammatory profile in the general population, but also to genetic particularities of the population [32, 33]. Additionally, a study in Brazil aimed at evaluating the anti-inflammatory impact of statins in urticaria observed changes in the proteome with a preponderance of inflammation type 1 [34]. A higher frequency of

atopy in CSU patients has also been reported in several studies [28, 35]; atopy in some LATAM populations was three times more frequent than the reported in North America and Europe in CSU patients, and double than the reported in the control population [35, 36]. Similar to what has been reported in other regions, CSU patients in LATAM have a higher incidence of hypothyroidism, Sjögren's Syndrome, arthritis and other autoimmune diseases [24, 37, 38].

From these findings, we can conclude that IgE mediation and inflammation type 2 are important topics for research in LATAM CSU patients, with certain peculiarities to what has been reported in other countries.

How the environment affects CSU? The observation that the frequency of inducible urticaria varies according to environmental conditions [39] suggests that it is possible that different environmental factors could influence chronic urticaria. In LATAM, the high frequency of endemic parasitosis, the diversity of climatic conditions, the high rates of poverty with an impact on living conditions, could be factors that influence the CSU incidence or severity; unfortunately, few studies evaluate these aspects. Borges J et al. observed that NSAID-hypersensitivity in patients with CSU was associated with greater atopy to house dust mites [40, 41].

Using In silico analysis, the potential cross-reactivity between environmental allergens, and the autoantigens (TPO, IL24 and Thyroglobulin) most frequently associated with CSU were evaluated [42]; the study did not find high structural similarities between the allergens and autoantigens, which suggest that it is unlikely that IgE mediation in CSU is secondary to a phenomenon of cross-reactivity with environmental proteins. This type of bioinformatics analysis is useful and cost/efficient to rationally explore

and choose promising lines of research, reducing the economic expenses of in vivo or in vitro studies, which is of great importance in low- and middle-income countries such as LATAM countries.

Knowledge gap Studies are needed in different LATAM populations evaluating the mechanisms of the disease and the prevalence of different endotypes, phenotypes and the implication of type 2 inflammatory predominance in the general population.

Recommendation Research centers of excellence in LATAM such as those led by the UCARE network are called to carry out collaborations to have a better knowledge of the impact of the environment, genetic ancestry and other CSU particularities. Further studies are needed to understand the mechanisms of the disease in the region and the factors associated with clinical outcomes such as response to pharmacological treatment and clinical evolution.

CSU treatment in LATAM

What is the treatment of CSU in LATAM in primary care? In Latin America, a significant lack of knowledge in the management of the disease has been detected among primary care physicians; 40% of patients with CSU referred to specialized urticaria centers by primary care physicians had not received treatment with antihistamines [43]; 35% had unnecessary restriction of activities, food or medications [7, 9, 10]. The request for unnecessary laboratory tests was also frequent [43]. These indicate a need to improve knowledge of urticaria by primary care physicians similar to what has been reported by some European countries [44, 45]. As a solution to this problem, several initiatives are being carried out in Ecuador that have been replicated in

Table 1 LATAM Particularities and recommendations for closing CSU knowledge gaps

#	LATAM population particularities	Gaps	Recommendations
Investigation opportunity	Diverse genetic ancestry High frequency of atopy, eosinophils, type 2 inflammation Diverse environmental conditions Parasites endemic regions and high frequency of tropical diseases	Unknown impact in CSU / CIndU	Multicentre investigations e.g., by UCARE network
Investigation Opportunity // Clinical barrier	High proportion of population living in rural area	Low access to urticaria therapies	The construction of local guidelines based on evidence from local research could improve health systems
Clinical barrier	High number of countries with low GDP Access to therapies like omalizumab High out of pocket expense		

CSU Chronic spontaneous urticaria, CIndU Chronic Inducible Urticaria, GDP Gross Domestic Product

other countries seeking to improve patient empowerment regarding their disease [46].

What is the treatment of CSU in LATAM among urticaria specialists? Despite the knowledge of international guidelines by specialists, in LATAM economic needs sometimes prevail over the clinical guideline's recommendations [8, 47]. Recently, among different UCARE groups in LATAM, an evaluation of the direct costs secondary to the treatment of CSU has been carried out, observing that in those countries with health system coverage of pharmacological therapies there is greater adherence to international guidelines while in the countries where out-of-pocket spending is required to access these therapies was high, compliance with the guidelines was lower, with the potential impact on disease control (<https://ga2len-ucare.com/projects/#current>). For example, in LATAM, the majority of urticaria specialists used the EAACI/GA²LEN/EuroGuiDerm/APAAACI guideline [3, 43], however, a multicenter study in LATAM reports the frequent use of Omalizumab 150 mg/month over Omalizumab 300 mg/month because in several countries it is not covered by the health system [48]. On the contrary, in countries where the health system covers the pharmacological therapies indicated for CSU, the guidelines recommendations are followed more frequently [1, 49].

Arias-Cruz and collaborators observed that treatment with antihistamines in conventional or higher doses could represent a high direct expense, being 5% to 30% of a current monthly minimum wage in Mexico [8]. In Brazil, treatment with omalizumab could represent several minimum monthly salaries for the patient, however, the feasibility of access occurred through the health system (Congress abstract <https://doi.org/https://doi.org/10.1016/j.waojou.2020.100389>). The cost of the disease is also reflected in the high impact on quality of life, lost work days and the greater prevalence of mental health illnesses such as anxiety and depression with the consequent social impact for the patient [8, 50, 51].

Conclusion

Table 1 summarizes some characteristics of the region, unmet needs and possible strategies for their future resolution. In the last 10 years, the number of studies in LATAM on CSU has increased significantly. The establishment in LATAM of centers of excellence in urticaria (UCARE) (<https://ga2len-ucare.com/centers/>) has allowed the creation of networks and the development of multicentric work comparing information within the region but also with other regions of the world. The published studies have made it possible to identify some

particularities of the region that could intervene in the development and response to treatment of the disease.

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 - In this study, the prevalence of CIndU is evaluated based on self-report but also through challenge tests.
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 - First study to evaluate the presence of Immunoglobulin E against eosinophil autoantigens.

Author contributions "JS, ICO and LA, give the central idea. All authors reviewed the manuscript."

Funding Open Access funding provided by Colombia Consortium. The study was supported by the Group of Clinical and Experimental Allergy, Hospital "Alma Mater de Antioquia" and the University of Antioquia (Medellín, Colombia).

Declarations

Competing interests The authors declare no competing interests.

Human and Animal Rights This is a review article. This article does not contain experiments with human or animal subjects performed by any of the authors.

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